UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/669,441	09/25/2003	Leland Shapiro	SHAP-000110	4274

68514 7590 10/04/2007

DON D. CHA
17225 W. 12TH AVE.
GOLDEN, CO 80401

EXAMINER	
BETTON, TIMOTHY E	
ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
10/04/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/669,441	SHAPIRO, LELAND	
	Examiner	Art Unit	
	Timothy E. Betton	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18 and 19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8 February 2005, 17 pages*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Claims 18 and 19 are pending for examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claim 18 and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Instant claim 18 fails to point out the identity of the composition's components by structure, formula or chemical name. In the absence of a structural formula or nomenclatorial description in the claims, the active agent to be used in the method claim has not been particularly pointed out or distinctly claimed.

Further, instant claim 18 is drawn to a method of inhibition of nitric oxide production by the contacting of a cell with at least one agent exhibiting mammalian α1-antitrypsin or serine protease inhibitor activity. However, the instant specification provides no adequate distinction of which particular agent or agents would be indicated for such inhibition *supra.*

Based on the embodiments of the instant specification in view of the instant claims, what is regarded, as applicants' invention is not clear. Further, the specification cites general extrapolations of chemical names, which allegedly exhibit mammalian inhibitor activity.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 18 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Amin et al. (USPN 5,789,395) and Mooney et al. (USPN 5885829) in view of Zhuang et al. (Growth and viability of macrophages continuously stimulated to produce nitric oxide, (1997), Proc. Natl. Acad. Sci USA, vol. 94, pp. 11875-11880, printed pages 1-3.

Amin et al. teach a *method for inhibiting endogenous production of nitric oxide (NO) in an in vivo, in vitro, or ex vivo mammalian system.* The method employs a *tetracycline compound* to inhibit production of NO and/or to inhibit the expression or activity of an inducible isoform of nitric oxide synthase (iNOS). Preferably, the tetracycline compound has inhibitory activity for metalloproteinases. Also it is preferred that the tetracycline compound is provided to the

mammalian system in an amount, which has little or no antibacterial activity in the system. Accordingly, preferred tetracycline compounds are tetracycline compounds which have be modified to reduce or eliminate their antimicrobial activity. The method can be used to treat medical conditions in mammals characterized by NO production mediated by iNOS, including, for example, inflammatory conditions (abstract only).

Amin et al does not teach serine protease and/or antitrypsin.

However, Mooney et al. teach methods for regenerating dental and oral tissues from viable cells using *ex vivo culture* on a structural matrix. The regenerated oral tissues and tissue-matrix preparations thus provided have both clinical applications in dentistry and oral medicine and are also useful in *in vitro* toxicity and biocompatibility testing (Abstract Only).

Mooney et al. teach general *serine protease inhibitor 3,4-dichloroisocoumarin* and the specific thiol reagent N-ethyl maleimide were shown to block apoptotic internucleosomal DNA cleavage in thymocytes without the involvement of endonucleases (Cain et al., 1994). The cysteine protease inhibitors E64 and leupeptin, the calpain selective inhibitor acetyl-leucyl-leucyl-normethional, and the serine protease inhibitors diisopropylfluorophosphate and phenylmethylsulfonyl fluoride were all shown to selectively block T-cell receptor-triggered programmed cell death in murine T-cell hybridoma and in activated peripheral T-cells (Sarin et al., 1993). Tetrodotoxin, nimodipine, verapamil, flunarizine and R56865 all protect bovine chromaffin cells from veratridine-induced cell death (Maroto et al., 1994). Caspase inhibitors are also contemplated for use as apoptosis inhibitors.

Zhuang et al. teach deregulated production of nitric oxide (NO) has been implicated in the development of certain human diseases, including cancer. We sought to assess the damaging

potential of NO produced under long-term conditions through the development of a suitable model cell culture system. In this study, we report that when murine macrophage-like RAW264.7 cells were exposed continuously to bacterial lipopolysaccharide (LPS) or mouse recombinant interferon-γ (IFN-γ) over periods of 21-23 days, they continued to grow, but with doubling times 2 to 4 times, respectively, longer than the doubling time of unstimulated cells. *Stimulated cells produced NO at rates of 30 to 70 nmol per million cells per day throughout the stimulation period.* Within 24 hr after removal of stimulant, cells resumed exponential growth. Simultaneous exposure to LPS and IFN-γ resulted in decreased cell number, which persisted for 2 days after removal of the stimulants. Exponential growth was attained only after an additional 4 days. Addition of *N*-methyl-L-arginine (NMA), an NO synthase inhibitor, to the medium inhibited NO production by 90% of all stimulated cells, partially reduced doubling time of cells stimulated with LPS or IFN-γ, and partially increased viability and growth rates in those exposed to both LPS and IFN-γ. However, when incubated with LPS and IFN-γ at low densities both in the presence and in the absence of NMA, cells grew at a rate slower than that of unstimulated cells, with no cell death, and they resumed exponential growth 24 hr after removal of stimulants. Results from cell density experiments suggest that macrophages are protected from intracellularly generated NO; much of the NO damaging activity occurred outside of the producer cells. *Collectively, results presented in this study suggest that the type of cellular toxicity observed in macrophages is markedly influenced by rate of exposure to NO: at low rates of exposure, cells exhibit slower growth; at higher rates, cells begin to die; at even higher rates, cells undergo growth arrest or die. The ability of RAW264.7 cells to produce NO over many cell generations makes the cell line a useful system for the study of other aspects of cellular damage,*

including genotoxicity, resulting from exposure to NO under long-term conditions (pages 1 and 2).

Essentially, Zhuang et al. teach that macrophages are cells, which are susceptible to producing nitric oxide based on the explanation *supra.*

Thus, it would be prima facie obvious to the skilled artisan at the time of invention to at once recognize the reasonable expectation of success via the combining or the incorporating together of teachings of Amin et al., Mooney et al. and Zhuang. Amin et al. teach methods that inhibit endogenous production of nitric oxide *in vivo, in vitro, or ex vivo* in a mammalian system. Mooney teach the specific inhibition of serine protease *in vivo* for biocompatibility testing or assaying. Zhuang et al. teach macrophages as cells, which are susceptible to producing nitric oxide. Likewise, these cells were studied in an *in vitro* culture. Instant claim 19 is made obvious by the same testing shared by the above references in relation to mammalian tissue and/ or cell cultures and mammalian biocompatibility organ testing.

Amin et al. teach the objective of claimed invention in addition to the central issue of claimed invention. Accordingly, Amin et al. serves as the motivation to combine both Mooney et al. and Zhuang et al. in obviousness over claimed invention.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Timothy E. Betton whose telephone number is (571) 272-9922. The examiner can normally be reached on Monday-Friday 8:30a - 5:00p. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be

reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

JAMES O. WILSON
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

TEB